

Wave nucleation rate in excitable systems in the low noise limit

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Motivated by recent experiments on intracellular calcium dynamics, we study the general issue of fluctuation-induced nucleation of waves in excitable media. We utilize a stochastic Fitzhugh-Nagumo model for this study, a spatially extended nonpotential pair of equations driven by thermal (i.e., white) noise. The nucleation rate is determined by finding the most probable escape path via minimization of an action related to the deviation of the fields from their deterministic trajectories. Our results pave the way both for studies of more realistic models of calcium dynamics as well as of nucleation phenomena in other nonequilibrium pattern-forming processes.

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One very important class of nonequilibrium spatially extended systems is that of excitable media. In these, a quiescent state is linearly stable but nonlinear waves can nonetheless propagate without decaying. These waves can be generated by above-threshold local perturbations and they also can become self-sustaining in the form of rotating spirals [1]. Examples of excitable media include many biological systems such as the cyclic adenosine monophosphate (cAMP) waves seen in *Dictyostelium* amoebae aggregation [2], electrical waves in cardiac and neural tissue [3], and, primary for our focus here, intracellular calcium waves [4].

Most excitable systems are sufficiently macroscopic as to render unimportant the role of thermodynamic fluctuations and allow for a description in terms of deterministic Partial Differential Equation (PDE) models. For these cases, noise effects can still be studied via the imposition of external variation in time and/or space (e.g., by varying illumination in a light-sensitive Belousov-Zhabotinsky (BZ) reaction [5–7]); however, there is no need to include noise in a description of the “natural” version of these systems. This is manifestly not the case for intracellular calcium dynamics; since the excitability here arises through the opening and closing of a small number of ion channels (allowing/preventing calcium efflux from calcium stores [8]), fluctuations are inherently nonnegligible. Indeed, experiments show direct evidence of noise effects in the form of abortive waves and spontaneous wave nucleation [9,10]. The mechanism leading to the nucleation of a calcium wave can be described as follows: A stochastic opening of some channels leads to an increased calcium concentration that favors the opening of additional channels. This activation will spread via diffusion and initiate a self-sustaining Ca^{2+} excitation wave. One could study this by using a very detailed model of calcium kinetics [11,12], but a general understanding should be obtainable using well-studied generic models for this type of stochastic excitable media, such as the Fitzhugh-Nagumo equations [13,14].

Thus, we study the process of spontaneous wave nucleation for a $1d$ excitable system modeled by the Fitzhugh-Nagumo equations.

$$\partial_t u = (3u - u^3 - v)/\epsilon + \nabla^2 u + \eta_u, \quad (1)$$

$$\partial_t v = u + (1 + \gamma) + \eta_v, \quad (2)$$

where η_v and η_u are noise terms. The particular form of these terms that would arise in a realistic model of intracellular calcium dynamics, as derived from a stochastic representation of release sites, will clearly involve multiplicative noise. Their exact form depends on the particular stochastic model used and is beyond the scope of this study (it will be addressed in further work). Here, for the sake of simplicity we choose η_v and η_u to be small independent white noise terms modeling fluctuation effects with covariance equal to

$$\langle \eta_i(x, t) \eta_j(x', t') \rangle = \beta \delta_{ij} \delta(x - x') \delta(t - t'). \quad (3)$$

At $\beta=0$ and for positive values of γ , this system is excitable with a single stable equilibrium point $u_0 = -(1 + \gamma), v_0 = 3u_0 - u_0^3$. As already mentioned, a wave of excitation can propagate through the system (see Fig. 1); a counter-propagating pair of such waves will be generated if a local perturbation above a threshold value is applied. For negative values of γ , the system becomes oscillatory. As already men-

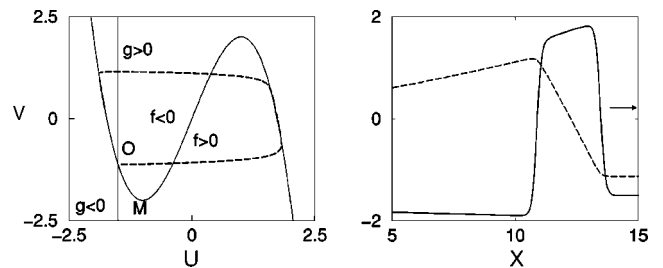


FIG. 1. Left: phase space diagram of the Fitzhugh-Nagumo system without noise and without the diffusive term. The stable equilibrium point is O . The $f(u, v) = 3u - u^3 - v$ nullcline is the S shaped solid line with minimum at M and the $g = u + (1 + \gamma)$ nullcline is the thin solid line. A small perturbation of O leads to a large excursion in phase space. The dashed line shows the phase space excursion of a point during the propagation of a single wave. Parameter values are $\gamma = 0.5$ and $\epsilon = 0.05$. Right: Typical propagating wave in an excitable medium. Solid line: u ; dashed line: v . The widths of the wave front and wave back [regions of fast change in u where (u, v) is not on the f nullcline] are of order $\sqrt{\epsilon}$. The full return to equilibrium is not shown.

tioned, this model is not meant to be a realistic approximation for calcium dynamics in any specific biological context; instead we use the model to understand the generic features of calcium wave nucleation due to noise.

Specifically, at finite β the noise will allow the birth of pairs of counter-propagating wave at a rate that will depend on the amplitude of the noise. That rate can be determined in the case of relatively high noise using direct numerical simulations. However, in the case of low noise, such a method becomes computationally prohibitive. Here we present a computation of the transition rate using a most probable escape path (MPEP) approach that is based on solving the Fokker-Planck equation [15,16]. This method has been successfully applied to dynamical systems [17,18] and to a few cases of spatially extended systems, namely the transition from creep to fracture [19] and magnetic domain reversal [20,21]. To derive the equation for the MPEP, we use the fact that the solution of the Fokker-Planck equation with given initial and final field configurations for time interval $[0, T]$ can be written in terms of the path integral

$$P(T) = \int \mathcal{D}u \mathcal{D}v \exp\left(-\frac{1}{\beta} \int \int dt dx S(x, t)\right), \quad (4)$$

with the ‘‘action density’’ S given by the sum of the squared deviations of the time derivatives of the fields from their deterministic values: $S \equiv \delta_u^2 + \delta_v^2$, where

$$\delta_u = \partial_t u - (3u - u^3 - v)/\epsilon - \Delta u, \quad (5)$$

$$\delta_v = \partial_t v - u - (1 + \gamma). \quad (6)$$

The functional integral is taken over all paths that begin at $t=0$ in equilibrium and end with a given final counter-propagating wave state (u_f, v_f) at $t=T$. Since we take β close to 0, the right-hand side of Eq. (4) is dominated by the path (called MPEP) that maximizes the integrand over all paths; thus, the transition rate is found to be proportional to

$$\exp(-E/\beta), \quad (7)$$

where E is the minimum over all paths of $\int dx \int dt S$. Therefore, in order to compute the transition rate between the rest state and a pair of counter-propagating waves, one has only to compute the minimum of the quantity in Eq. (4). This minimum can be expressed using a variational principle as the solution of a partial differential equation (PDE) [22]; however, using this approach to find the actual MPEP between two different states involves the use of a shooting method with numerous parameters, which turns out to be numerically quite difficult. Instead, we used an alternative method based on discretizing the above path integral on a space-time grid and directly using a quasi-Newton [23] method to find the minimum. One difficulty with this approach is that the Fitzhugh-Nagumo model has a slow recovery time compared to the time scale associated with a pulse [(width of pulse)/speed]. This then necessitates having a very large spatial domain, if one attempts to completely encompass the region over which the nucleated wave configuration differs from the quiescent fixed point. To get around this

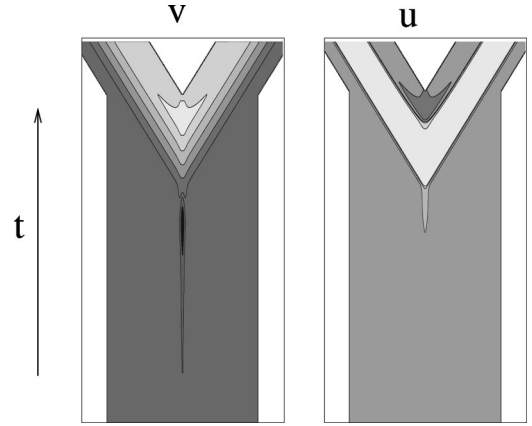


FIG. 2. Space time contour plot of the u (right) and v (left) field during nucleation with $T=20$; parameter values are $\epsilon=0.1$ and $\gamma=0.2$. Time increases upward and the white area corresponds to the region outside of $[x_{\min}(t)=\max(x_f(t)-x_{\text{off}},0); x_{\max}(t)=\max(L+x_f(t)-x_{\text{off}},0)], [0, T]$. The contours are at $-2, -1, 0$, and 1 for the u field and at $v_0-0.2, v_0-0.05, v_0+0.05, v_0+1, v_0+2$, and v_0+3 for the v field. The lighter the surface, the higher the values of the fields are; thus, the light region of the u contour plot corresponds to the excited region. After the nucleation event, points near the center reach the maximum of the excited branch of the f nullcline (see Fig. 1), return to the quiescent state and thereby give birth to the two wave backs.

difficulty, we use a grid moving with the pulse. That is, the grid moves in the same direction as the pulse in order to keep the wave front at a fixed distance from the boundary. Thus, the boundaries of the domain used to compute the MPEP are no longer $[0, L], [0, T]$, but $[x_{\min}(t)=0+\max(x_f(t)-x_{\text{off}},0), x_{\max}(t)=L+\max(x_f(t)-x_{\text{off}},0)], [0, T]$, where $x_f(t)$ is the position of the wave front defined as the point where u goes above 0 and x_{off} is an arbitrary value lower than L and significantly bigger than the width of the wave front. The following boundary conditions are applied:

$$\begin{aligned} &\text{at } x=x_{\max}(t): u=u_0, \quad v=v_0, \\ &\text{at } x=x_{\min}(t) \begin{cases} \partial_x u(0)=0 & \text{if } x_{\min}(t)=0 \\ \delta_u(0)=0 & \text{if } x_{\min}(t) \neq 0. \end{cases} \end{aligned} \quad (8)$$

The condition $\delta_u=0$ implies that the recovery past x_{\min} is purely deterministic and hence does not contribute to E . A check on our procedure is afforded by the fact that as long as the distance the wave had traveled (in the final state) is significantly bigger than the region over which the wave initiates, the results obtained are independent of both the distance the wave had traveled and the width of the space window used (L). We fix T to be large enough that the deviation from deterministic dynamics for very small time is negligible. Once T is fixed and the specific final wave state chosen, there is no time-translation invariance in the MPEP.

We now describe the results obtained using this methodology. In the small ϵ limit ($\epsilon < 0.1$), the shape of the MPEP is quantitatively independent of ϵ and γ and even for high values of ϵ , there is no significant qualitative difference. In Fig. 2, we present such a typical escape path. As shown on

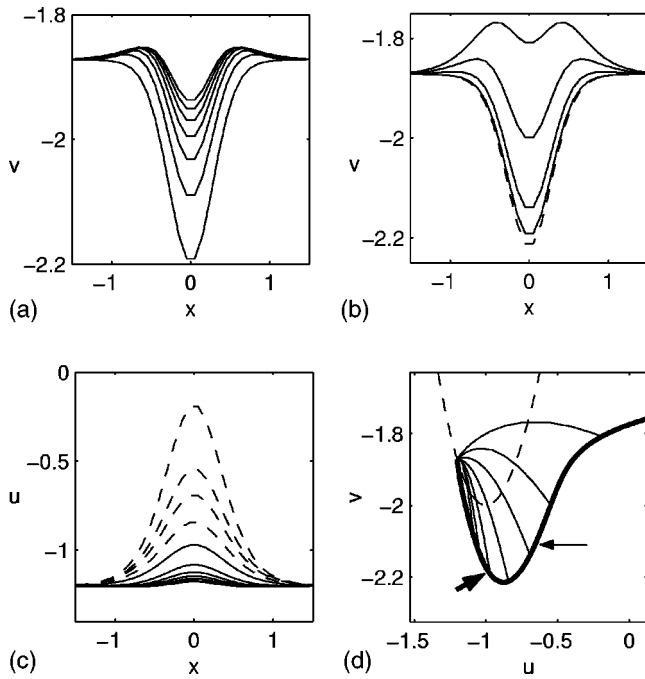


FIG. 3. (a) and (b) v profiles during a typical nucleation event. (a) v profiles at times 25, 25.5, 26, 26.5, 27, 27.5, and 28. During that stage, the minimal value of the v field decreases. (b) v profiles at times 28 (dashed), 28.25, 28.5, 28.75, and 29 (solid lines). During this stage, the minimal value of v increases. (c) u profiles at the same times. The profiles corresponding to the (a) and (b) curves are represented with a solid, dashed line. (d) The dashed line represents the f nullcline. The thick solid line is the trajectory in the phase plane $[u(x=0,t), v(x=0,t)]$ of the center of nucleation. The point where maximum value of $\int dx(\delta_u^2 + \delta_v^2)$ is reached is indicated by a thick arrow, whereas the point where this deviation is below 1% of this maximal value is indicated by the thin arrow. Beyond this point the dynamics are mainly driven by the deterministic equations. The thin solid lines represent spatial snapshots of the MPEP $[u(x,t=T_i), v(x,t=T_i)]$ profile at regularly spaced points in time $(T_i - T_{i-1} = 0.5)$.

the contour plots, wave nucleation is found to be a very localized event. Essentially, the noise acts to create a local dip in value of the v field which is then followed by a large positive excursion for the u field as it goes into the excited phase. To describe this mechanism more fully, we present in Fig. 3 the phase-plane trajectory at the center of nucleation as well as several snapshots of the spatial form of the fields during the nucleation process. One can see then that the escape path consists of the center of nucleation being driven by noise below the minimum of the f nullcline; this then quickly drives the u field positive and leads after v -field driven relaxation, to the pair of counter-propagating pulses. There is a significant fluctuation contribution to the nucleation event in a small region around the nucleation point (see Fig. 4). Results using different values of γ and ϵ show that the width of this small region is proportional to the width of a front, that is $\sqrt{\epsilon}$ (see Fig. 5). Note that the other simple possibility that of nucleating an excited region for the u field at a fixed value of v [24] is not observed.

In accord with the shape of the trajectory, our calculations

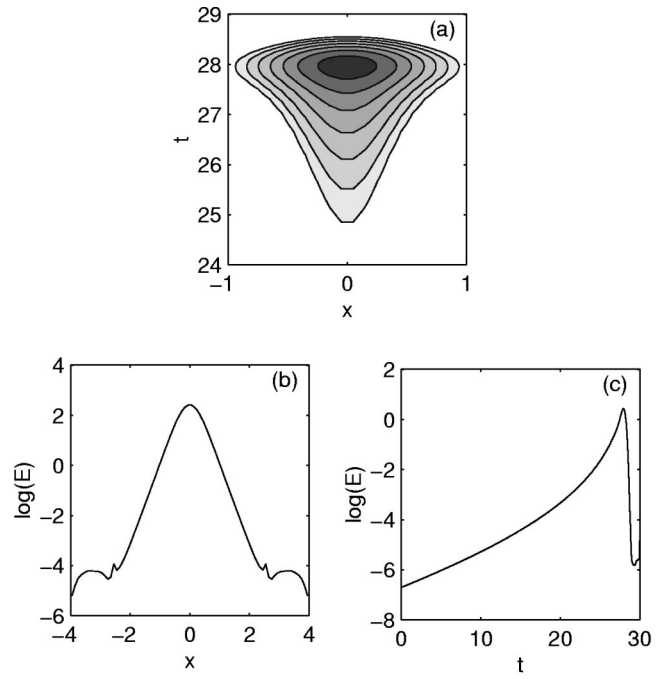


FIG. 4. Parameter values are $\epsilon=0.1$ and $\gamma=0.2$. (a) Space time contour plot of the action density $\delta_u^2 + \delta_v^2$ with its maximal value normalized to one. The contours are at $1/96, 1/48, 1/24, 1/12, 1/6, 1/3,$ and $1/1.5$. (b) Spatial distribution $[\int dt(\delta_u^2 + \delta_v^2)]$ of the contribution to $\log_{10}(E)$ during the MPEP. (c) Temporal distribution $[\int dx(\delta_u^2 + \delta_v^2)]$ of the contribution to $\log_{10}(E)$ during the MPEP. One can see that the contribution to E as a function of time increases exponentially and then decreases rapidly to a very low level that is close to numerical noise.

show that the main contribution to E during the MPEP come from the $\int \delta_v^2$, at least for small values of ϵ —this is true for all γ although there is a (weak) γ dependence. Thus for $\gamma = 0.2$ the value of the ratio $\int \delta_v^2 / \int \delta_u^2$ was approximately 30 for $\epsilon=0.1$, and went up to 1000 for the minimal value of ϵ used ($\epsilon=0.001$). For higher values of ϵ , the ratio was significantly lower (3 for $\epsilon=0.8$, close to the limit of propagation for this value of γ). Furthermore for small ϵ , E scales like $\sqrt{\epsilon}$ (see Fig. 5). For higher values of ϵ , this simple

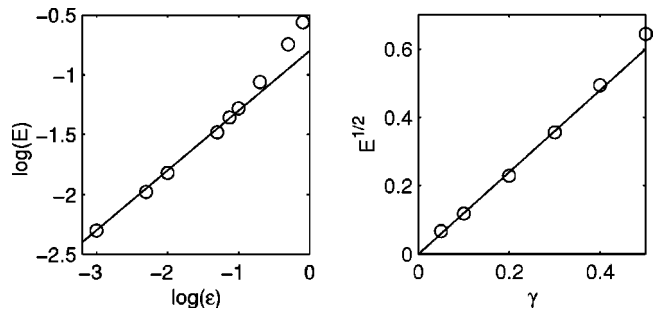


FIG. 5. Left: circles $\log_{10}\epsilon$ dependence of $\log_{10}E$ using a log scale, solid line: $y=x/2-0.8$. For small ϵ , E behaves like $\sqrt{\epsilon}$. Right: circles γ dependence of \sqrt{E} for $\epsilon=0.1$. Solid, $y=1.2x$. E behaves like γ^2 for a wide range of values of γ . The scaling breaks down for higher values of γ , close to the propagation threshold (for this value of ϵ , the threshold is at $\gamma=0.5525 \pm 0.0005$).

scaling is no longer valid. The fact that for small values of ϵ , E scales like $\sqrt{\epsilon}$ and that a wave is therefore much easier to nucleate can be explained by a simple argument. As already mentioned, the phase-plane trajectory of the MPEP is mainly independent of the value of ϵ . The only dependence is then due to the spatial scale appearing in the integral which is $\sqrt{\epsilon}$, giving rise to the observed result.

We now describe results obtained when varying γ with ϵ held constant. This means that we consider the nucleation rates for differing excitabilities but with the same ratio of time scales between the u and v field dynamics. For a wide range of values of γ , we find that E scales like γ^2 (see Fig. 5). The more excitable the system, the more likely it is to nucleate a wave. This scaling is the same as one would obtain analytically in the much simpler zero-dimensional(0D) version of this problem. Here the analog of wave nucleation is the noise-induced creation of a large transient excursion away from the fixed point. If ϵ is small, the escape path will follow the f nullcline down to its minimum and then follow the noiseless dynamics to reach the other stable branch. In such a situation, one can compute the transition rate analytically in a piecewise linear version of the FH model [25]:

$$\dot{u} = \begin{cases} -\frac{1}{\epsilon}(v+u) & \text{if } u < 0, \\ \frac{1}{\epsilon}(1-v-u) & \text{if } u \geq 0, \end{cases} \quad (9)$$

$$\dot{v} = u + \gamma. \quad (10)$$

In this model, the equilibrium point is $u_0 = -\gamma$, $v_0 = \gamma$. The branch $u < 0$, $u+v=0$, corresponds to the left hand side branch of $f(u,v)=0$ in the phase diagram of the 0D FH system (see Fig. 1), the point $u=v=0$ corresponds to the minimum of this branch and the branch $u > 0$, $u+v=1$ corresponds to the right hand side branch of the f nullcline in Fig. 1. A long excursion in the phase space will occur as soon as u becomes positive. Since ϵ is taken to be small, the path that minimizes the action follows the analog of the left hand side branch of the f nullcline, that is, the line of equation $u+v=0$ from the equilibrium point to the point where u becomes positive. This allows us to eliminate the contribution of the deviation from the deterministic equation governing the evolution of u in the action of the escape path and to consider that the system remains on the line of equation $u+v=0$ (note that this latter assumption is only valid as long as the time scale of the escape path is much longer than the characteristic time scale of the evolution equation of u).

Then it can be easily shown that the variational equation for the MPEP has the form

$$\frac{d^2v}{dt^2} = v - \gamma, \quad (11)$$

with $v(0)=v_0=\gamma$ and $v(T)=0$. A straightforward calculation shows that the action is equal to

$$\gamma^2 \frac{2}{1 - \exp(-2T)} \quad (12)$$

and that its minimum, reached for $T=\infty$, is equal to $2\gamma^2$. This result obtained from a zero-dimensional approach shows that the γ^2 scaling of E found in our computations can be interpreted as being due to γ equaling the ‘‘distance’’ of the stable equilibrium point from the border of its basin of attraction or the distance of the system from an oscillatory system since for $\gamma=0$, the FH system undergoes a Hopf bifurcation and becomes oscillatory.

Putting it all together, our data yield a log transition rate decreasing linearly with $-\gamma^2\sqrt{\epsilon}/\beta$. This result could be tested experimentally, perhaps by adding illumination noise to the light-sensitive BZ reaction. In the case of the intracellular calcium dynamics, despite the loose connection between the FH model parameters and the parameters governing the behavior of intracellular Calcium, our results can be used in the vicinity of the transition from an excitable regime to an oscillatory regime. Indeed, in this situation, the parameter γ being the distance between the system and the Hopf bifurcation point, can be linked to the IP3 concentration which likewise governs the transition to an oscillatory regime.

It is worth mentioning that there are other potential applications of the MPEP approach to nucleation in spatially extended nonequilibrium systems. One example concerns the thermal generation of localized patches of traveling rolls in electroconvection [26]. Also, the method used here is not limited to white noise. A simple generalization of the derivation allows for the incorporation of multiplicative noise via dividing the δ_u^2 and δ_v^2 terms in the action density by the corresponding (possibly field dependent) variances of the noises added to the u and v equations, respectively. Finally, there is a similarity between the MPEP method and what must be done to consider quantum tunneling in spatially extended systems [27], where one also must find the entire space-time path tunneling trajectory in order to find a leading estimate of the rate.

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